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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/770,294	02/02/2004	Andrew D. Miller	YOUZ 2 00059-2	1414

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EXAMINER	
FORD, VANESSA L	
ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 05/04/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/770,294	MILLER ET AL.	
	Examiner	Art Unit	
	Vanessa L. Ford	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 23-70* is/are pending in the application.

4a) Of the above claim(s) *1* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *2 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/23/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's response to the restriction requirement, the election of Group II, claims 23-70 filed on January 18, 2005 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 2-22 have been cancelled. Claim 1 is withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Priority

2. Acknowledgment is made of applicant's claim for foreign priority based on an application foreign applications United Kingdom 9705498.5, 03/17/1997 and United Kingdom 9610944.2, 5/24/1996. However, applicant has not filed a certified copy of the United Kingdom applications as required by 35 U.S.C. 119(b). Therefore, the priority benefit to this applications is not given. A copy of the documents must be submitted.

Claim Objection

3. Claim 68 is objected to for the following informality: "nucleotide" should be changed to "nucleotide". Correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 23-70 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to a method for treating a genetic disorder or condition or disease in a patient in need of treatment comprising administering an effective amount of a compound comprising a cholesterol group or derivative thereof having linked thereto a head group, wherein the head group is more positive than the head group of DC-Chol; further wherein the head group is a straight chain polyamine; further wherein two or more of the amine groups of the polyamine are separated by an ethylene group.

The claims broadly encompasses gene therapy, wherein the claimed method of treating a genetic disorder or condition or disease, is treated by administering a cationic lipid compound admixed with or associated with a nucleotide sequence.

The specification teaches that the compound of the invention is used in gene therapy, especially gene transfer (page 1). The specification teaches that one aspect of gene therapy involves the introduction of foreign nucleic acid into cells so that it is

expressed protein may carry out a desired therapeutic function (page 1). The specification teaches that this type of therapy includes the insertion of TK, TSG or ILG gene to treat cancer, the insertion of the CFTR gene to treat cystic fibrosis, the insertion of the NGF, TH or LDL genes to treat neurodegenerative and cardiovascular disorders, the insertion of the IL-1 antagonist gene to treat rheumatoid arthritis, the insertion of the HIV antigens and the TK genes to treat AIDS and CMV infections, the insertion of antigens and cytokines to act as vaccines and the insertion of β-globin to treat haemoglobinopathic conditions such as thalassaemias (page 1). There are no working examples in the instant specification to guide the skilled artisan in practicing the claimed method.

The state of the art for gene therapy as discussed by Vile et al *(Gene Therapy, Vol. 7, pp. 2-8, 2000)* is unpredictable. Vile et al teach that the problems in which gene therapy for cancer will take into the next millennium focus far less on the choice of therapeutic gene(s) to be used than on the means of delivering them. Vile et al teach that there is already a battery of genes that we know are very effective in killing cells and if these genes can be expressed at the right site and at appropriate levels therapy may be occur (page 2). However, until the perfect vector is developed, the choice of gene will remain crucially important in order to compensate for the deficiencies of the vectors we currently have available (page 2, 1st paragraph, left column). Vile et al teach that whatever its mechanism, no single genes can be a serious contender unless it has a demonstrable bystander effect (page 2, right column) and the requirement for such a bystander effect stems directly from the poor delivery efficiency provided by current

vectors (page 2, right column). Vile et al teach that a genuine ability to target delivery systems to tumor cells distributed widely throughout the body of a patient would simultaneously increase real titers and efficacy. Vile et al teach that in truth, no such systemically targeted vectors exist yet. Vile et al teach that injection of vectors into the bloodstream for the treatment of cancer requires not only that the vectors be targeted (to infect only tumor cells) but also that they by protected (from degradation, sequestration or immune attack) for long periods of time so that they can reach the appropriate sites for infection. Moreover, having reached such sites, the vectors must be able to penetrate into the tumor from the bloodstream before carrying out their targeted infection (page 4, bottom left column and top right column). In addition, Rochlitz C. F. *(Swiss Medicine Weekly, 131:4-9, 2001)* teaches that none of the more than one hundred clinical studies performed so far had formally proven efficacy of the approach (gene therapy) in any human disease. Rochilitz teaches that although anecdotal reports of tumor responses are becoming more frequent in several human malignancies, the situation has not changed dramatically." (see page 8, bottom of page). Rochlitz teaches that the main problems are still the lack of vectors with high transduction efficiency *in vivo*, the low tumor specificity of available systems, and our incomplete knowledge of molecular tumor pathology" (pages 8-9).

Thus, as taught above the state of the art regarding gene therapy is considered highly unpredictable. Furthermore, it would take one skilled in the art an undue amount of experimentation to determine what route of administration (e.g. intravenous, dermal, nasal, rectal, vaginal, inhalation, or topical administration) would result in a therapeutic

response using a recombinant virus, lentivirus, adenovirus, retrovirus or bacterium comprising the nucleic acid encoding the antigen. The state of the art regarding the route of administration for gene therapy as exemplified by Verma et al, (*Nature, Vol. 389, No. 6648, pages 239-242, 1997)*, indicates that factors including the nature of the diseases and/or disorders, the nature of a DNA and/or target tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo* must be considered for any gene therapy method to be successful (page 238, columns 1 and 2). Therefore, the skilled artisan at the time the invention was made recognized the lack of predictability of the nature of the art and state of the prior art to which the instant invention pertains. .Also, such disclosures clearly indicate that the amount of direction or guidance presented in the specification is limited, and would not permit a person skilled in the art to use the invention without undue experimentation at the time the invention was made.

In view of the lack of predictability of the art to which the invention pertains, the lack of established clinical protocols for effective gene therapies, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for treating a genetic disorder, or condition or disease in a patient.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 22-70 recite the term "associated with". It is unclear as to what the applicant is referring? Clarification as to the meaning of this phrase is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

It should be noted that the prior art document WO96/10038, published April 4, 1996 are set forth under 35 U.S.C. 102(b) because Applicant has not perfected the priority to foreign applications. See paragraph 2 above. In the event the Applicant perfects the priority to the foreign application the rejections will be held under 35 U.S.C. 102(a).

6. Claims 23-70 are rejected under 35 U.S.C. 102(b) as anticipated by Boutin *(WO 96/10038 published April 4, 1996)* or in the alternative under 35 U.S.C. 102(a).

Claims 23-70 are directed to a method for treating a genetic disorder or condition or disease in a patient in need of treatment comprising administering an effective amount of a compound comprising a cholesterol group or derivative thereof having linked thereto a head group, wherein the head group is more positive than the head group of DC-Chol; further wherein the head group is a straight chain polyamine; further wherein two or more of the amine groups of the polyamine are separated by an ethylene group.

Boutin teaches a method of immunizing an individual against a pathogen by administering to an individual the multifunctional molecular complex of the invention comprising a nucleic acid composition and a transfer moiety (see the Abstract and page 37). Boutin teaches that the nucleic acid composition is administered to cells comprising a nucleotide sequence that encodes a peptide which comprises at least an epitope identical to or substantially similar to an epitope displayed on said pathogen as antigen and said nucleotide sequence that is operatively linked to regulatory sequence (page 37). Boutin teaches that the method of immunizing an individual against a hyperproliferative disease or autoimmune disease (pages, 14-15, 37 and 50-51). Boutin teaches that the compositions administered in the method of immunizing of the invention include pharmaceutically acceptable salts or ester together with a pharmaceutically acceptable carrier (page 38). Boutin teaches that the invention can be

used to combat cancer (page 39). Boutin teaches that the multifunctional molecular complex used in the methods of the invention comprises a nucleic acid composition, a transfer moiety comprising one or more cationic polyamine components bound to said nucleic acid composition and one or more endosome membrane disruption promoting components attached to at least one nitrogen atom of at least one said polyamine components through for example, carbamoyl bridging groups and for example a cholesteryl or derivatives thereof (pages 12-13). Boutin teaches that the transfer moiety comprises an endosome disruption promoting component that can comprise cholesterol (page 27). Boutin teaches that the endosome disruption promoting component is bounded to the cationic polyamines (see the Abstract). This component of the transfer moiety meets the claim limitation "wherein the cholesterol group or derivative is cholesterol". Boutin anticipates the claimed invention.

Since the Office does not have the facilities for examining and comparing applicant's method with the method of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed method and the method of the prior art (i.e., that the method of the prior art does not possess the same material method steps and parameters of the claimed method). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

7. Claims 23-70 are rejected under 35 U.S.C. 102(e) as anticipated by Boutin *(U.S. Patent No. 5,837,533 published November 17, 1998).*

Claims 23-70 are directed to a method for treating a genetic disorder or condition or disease in a patient in need of treatment comprising administering an effective amount of a compound comprising a cholesterol group or derivative thereof having linked thereto a head group, wherein the head group is more positive than the head group of DC-Chol; further wherein the head group is a straight chain polyamine; further wherein two or more of the amine groups of the polyamine are separated by an ethylene group.

Boutin teaches a method of immunizing an individual against a pathogen by administering to an individual the multifunctional molecular complex of the invention comprising a nucleic acid composition and a transfer moiety (see the Abstract and column 25). Boutin teaches that the method of immunizing an individual against a hyperproliferative disease or autoimmune disease (columns 25-27). Boutin teaches that the compositions administered in the method of immunizing of the invention include pharmaceutically acceptable salts or ester together with a pharmaceutically acceptable carrier (column 30). Boutin teaches that the invention can be used to combat cancer (columns 25-26). Boutin teaches that the invention can be used to combat HIV (column 30). Boutin teaches that the multifunctional molecular complex used in the methods of the invention comprises a nucleic acid composition, a transfer moiety comprising one or more cationic polyamine components bound to said nucleic acid composition and one

or more endosome membrane disruption promoting components attached to at least one nitrogen atom of at least one said polyamine components through for example, carbamoyl bridging groups and for example a cholesteryl or derivatives thereof (see the Abstract). Boutin teaches that the transfer moiety comprises an endosome disruption promoting component that can comprise cholesterol (column 15). Boutin teaches that the endosome disruption promoting component is bounded to the cationic polyamines (see the Abstract). This component of the transfer moiety meets the claim limitation "wherein the cholesterol group or derivative is cholesterol". Boutin anticipates the claimed invention.

Since the Office does not have the facilities for examining and comparing applicant's method with the method of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed method and the method of the prior art (i.e., that the method of the prior art does not possess the same material method steps and parameters of the claimed method). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Pertinent Prior Art

8. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure *(WO 96/01840 published January 25, 1996 and US Patent No. 5,767,099 published June 16, 1998).*

Status of Claims

9. No claims are allowed.

Conclusion

10. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 872-9306.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (571) 272-0857. The examiner can normally be reached on Monday – Friday from 9:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (571) 272-0864.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov./>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Biotechnology Patent Examiner
April 22, 2005

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